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EXAMINER	
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1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/792,376	SABETSKY, VLADIMIR	
	Examiner	Art Unit	
	Ronald T. Niebauer	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-37 and 41-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-37 and 41-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The finality of the previous office action has been withdrawn.

Applicants amendments and arguments filed 10/10/07 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 1-25,38-40 have been cancelled.

Claims 26-37,41-45 are under consideration.

Claim Objections

Applicant is advised that should claim 43 be found allowable, claim 26 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicant is advised that should claim 45 be found allowable, claim 42 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-37,41-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.
>
> Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:
>
> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been

placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to compositions comprising crystallized dextran microparticles and insulin.

(1) Level of skill and knowledge in the art:

The level of skill in the art is high.

(2) Partial structure:

Section 0067 states that the term "insulin" shall be interpreted to encompass insulin analogs among other things. In section 0068 the term "insulin analog" is defined to be an insulin wherein one or more of the amino acids has been replaced with an alternative amino acid, one or more of the amino acids has been deleted, or wherein one or more additional amino acids has been added to the polypeptide chain. In section 0069 it is stated that the analogs are used to refer to molecules which share a common functionality and share typical structural features.

No direction is provided in the specification as to which amino acids can be deleted, substituted, or added. In considering the possible variability in the genus, it is noted that human insulin contains 51 amino acids (30 on the B chain and 21 on the A chain). If one simply considered replacing any of the 51 amino acids with any two different amino acids there would be 2^{51} (well over a trillion) different amino acids sequences. Further, if one considered other replacements, or deletions, or additions, the size of the genus is even larger. Hence, there is substantial variability in the genus.

In the specification (section 0036 and Table 1), the references are to insulin, presumably wild-type insulin. In section 0068, US 5,547,929 is incorporated by reference and cited as exemplary of insulin analogs. However, US 5,547,929 is drawn to a very limited subset of

analogs, specifically mutations at the 28 and 29 positions of the B chain. This reference is not representative of any and all analogs as defined in the instant specification. For example, neither the instant specification nor the incorporated reference discuss substitutions of any of the cysteines of insulin that are involved in disulfide bonding.

Since there are a substantial variety of polypeptides possible within the genus, the examples do not constitute a representative number of species and do not sufficiently describe the genus claimed (see Gostelli above).

(3) Physical and/or chemical properties and (4) Functional characteristics:

In section 0069 it is stated that the analogs are used to refer to molecules which share a common functionality and share typical structural features. However, this does not clearly set forth what possible analogs are part of the instant invention. No 'typical structural features' are recited. No common sequence is taught for all the analogs. There is no disclosed correlation between structure and function.

(5) Method of making the claimed invention:

The specification (section 0036 and Table 1) describes the use of insulin in the instant invention, however the specification fails to describe a representative number of analogs.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that the claim(s) is/are broad and generic, with respect to all possible analogs encompassed by the claims. The possible structural variations are many. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation

between function and structure of the analogs. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus. While having written description of analogs identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of analogs embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26-29,32,35,37,41-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Schroder (Methods in Enzymology 1985 as cited in IDS).

Schroder teach (page 123) a composition comprising insulin in a crystallized carbohydrate sphere which is made from a solution of dextran T10. Schroder teach that the term crystallization is meant to include hydrogen, and van der Waals interactions, for example (page 119) (compare claim 27 of the instant invention). Using biological assays, Schroder teach that 70% of the radioactivity is entrapped showing that 70% of the insulin is entrapped (page 122 1st full paragraph and page 123). As such, 30% of the insulin is not entrapped. Schroder specifically teach that proteins are not always fully entrapped (page 122 2nd full paragraph). Further, Schroder teach (Figure 2) that all of the insulin is not entrapped as significant portions of the insulin are released over time. Schroder teach aqueous solutions (page 121 last paragraph first sentence) (compare claim 28 of the instant invention). Schroder teach administration via injection (Figure 3 and page 124 last paragraph), so a vessel (such as a syringe) is necessarily required (compare claims 29,35 of the instant invention).

Claim 44 recites a wherein clause (see MPEP 2111.04) that requires the composition to include insulin that is not encapsulated by the microparticles. It is noted that the wherein clause of claim 44 does not specify the degree of encapsulation or how much of the insulin is not encapsulated. Using biological assays, Schroder teach that 70% of the radioactivity is entrapped (in a dextran insulin composition) showing that 70% of the insulin is entrapped (page 122 1st full paragraph and page 123). As such, 30% of the insulin is not entrapped. Schroder specifically teach that proteins are not always fully entrapped (page 122 2nd full paragraph). Further, Schroder teach (Figure 2) that all of the insulin is not entrapped as significant portions of the insulin are released over time. In summary, Schroder teach the components of claim 44

(crystallized dextran and insulin) as well as meet the limitation of the wherein clause (i.e. at least some of the insulin is not encapsulated).

Claims 41,43, and 45, for example recite properties (porosity and microparticle diameter) that are not reported by Schroder. Please note, since the Office does not have the facilities for examining and comparing Applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. *See In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980), and "as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). In the instant case, the claim product and prior art product are substantially identical in composition (i.e. comprise crystallized dextran and insulin) so a prima facie case of anticipation has been established (see MPEP section 2112.01 I).

Claims 32 and 37 recite compositions comprising shells. Based on the broadest reasonable interpretation of the claim (see MPEP 2111), the insulin entrapped in the crystallized dextran (see page 123) would be a shell meeting the claim limitations.

Claims 42 and 45 recite contacting of insulin with a surface of the dextran. Since the claims are open to any surface of the dextran, Figure 1 of Schroder shows that the protein is in contact with surfaces of the dextran thereby meeting the claim limitations.

Claims 26-29,32,35,37,41-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Schroder (US 4,713,249 as cited previously).

Schroder (the same author as cited above) teach compositions comprising dextran and insulin (claims 1,4,7). Schroder specifically teach the use of crystallized dextran (abstract, column 2 lines 54-58) which is defined to include hydrogen bonds (compare claim 27 of the instant invention). Schroder teach in example 13 a specific dextran insulin composition. Schroder teach sphere sizes within that of the instant invention (column 5 line 18-20) (compare claim 41 of the instant invention). Schroder teach that release experiments were performed so a vessel is necessarily present (example 13) (compare claims 29,35 of the instant invention). Schroder teach that insulin is released so that all of the insulin is not encapsulated (example 13). Schroder teach aqueous solutions (example 13) (compare claim 28 of the instant invention)

Claim 44 recites a wherein clause (see MPEP 2111.04) that requires the composition to include insulin that is not encapsulated by the microparticles. It is noted that the wherein clause of claim 44 does not specify the degree of encapsulation or how much of the insulin is not encapsulated. Schroder teach (example 13) that all of the insulin is not entrapped as significant portions of the insulin are released over time. In summary, Schroder teach the components of claim 44 (crystallized dextran and insulin) as well as meet the limitation of the wherein clause (i.e. at least some of the insulin is not encapsulated).

Claims 43, and 45, for example recite properties (porosity) that are not reported by Schroder. Please note, since the Office does not have the facilities for examining and comparing

Applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. *See In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980), and "as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). In the instant case, the claim product and prior art product are substantially identical in composition (i.e. comprise crystallized dextran and insulin) so a prima facie case of anticipation has been established (see MPEP section 2112.01 I).

Claims 32 and 37 recites compositions comprising shells. Based on the broadest reasonable interpretation of the claim (see MPEP 2111), the insulin entrapped in the crystallized dextran (see example 13) would be a shell meeting the claim limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schroder (Methods in Enzymology 1985 as cited in IDS) as applied to claims 26-29,32,35,37,41-45 above, and further in view of Moriyama (Journal of Controlled Release 1996 as cited in IDS).

As discussed above, Schroder teach (page 123) a composition comprising insulin in a crystallized carbohydrate sphere which is made from a solution of dextran T10. Schroder teach that the term crystallization is meant to include hydrogen, and van der Waals interactions, for example (page 119) (compare claim 27 of the instant invention). Using biological assays, Schroder teach that 70% of the radioactivity is entrapped showing that 70% of the insulin is entrapped (page 122 1st full paragraph and page 123). As such, 30% of the insulin is not entrapped. Schroder specifically teach that proteins are not always fully entrapped (page 122 2nd full paragraph). Further, Schroder teach (Figure 2) that all of the insulin is not entrapped as significant portions of the insulin are released over time. Schroder teach aqueous solutions (page 121 last paragraph first sentence) (compare claim 28 of the instant invention). Schroder teach administration via injection (Figure 3 and page 124 last paragraph), so a vessel (such as a syringe) is necessarily required (compare claims 29,35 of the instant invention).

Claim 44 recites a wherein clause (see MPEP 2111.04) that requires the composition to include insulin that is not encapsulated by the microparticles. It is noted that the wherein clause of claim 44 does not specify the degree of encapsulation or how much of the insulin is not encapsulated. Using biological assays, Schroder teach that 70% of the radioactivity is entrapped (in a dextran insulin composition) showing that 70% of the insulin is entrapped (page 122 1st full paragraph and page 123). As such, 30% of the insulin is not entrapped. Schroder specifically teach that proteins are not always fully entrapped (page 122 2nd full paragraph). Further,

Schroder teach (Figure 2) that all of the insulin is not entrapped as significant portions of the insulin are released over time. In summary, Schroder teach the components of claim 44 (crystallized dextran and insulin) as well as meet the limitation of the wherein clause (i.e. at least some of the insulin is not encapsulated).

Claims 41,43, and 45, for example recite properties (porosity and microparticle diameter) that are not reported by Schroder. Please note, since the Office does not have the facilities for examining and comparing Applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. *See In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980), and "as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). In the instant case, the claim product and prior art product are substantially identical in composition (i.e. comprise crystallized dextran and insulin) (see MPEP section 2112.01 I).

Claims 32 and 37 recite compositions comprising shells. Based on the broadest reasonable interpretation of the claim (see MPEP 2111), the insulin entrapped in the crystallized dextran (see page 123) would be a shell meeting the claim limitations.

Claims 42 and 45 recite contacting of insulin with a surface of the dextran. Since the claims are open to any surface of the dextran, Figure 1 of Schroder shows that the protein is in contact with surfaces of the dextran thereby meeting the claim limitations.

Schroder does not expressly teach PEG in the composition.

Moriyama teach (page 238 last paragraph) a solution of PEG and dextran with insulin. It is noted that in the embodiment of section 2.2 (page 238-239) and section 3.1 (page 240) that there is no cross-linking of the dextran. Moriyama teach that two-phase systems are useful for protein delivery (page 238 column 1). Moriyama teach that insulin will preferentially partition into the PEG phase (page 238 first full paragraph). Moriyama teach that the PEG-dextran two-phase system may exhibit degradation-controlled protein release and prevent drug diffusion (page 238 first column).

Schroder also teach compositions for slow release and targeting (title), specifically with dextran and insulin. One would be motivated to additionally use PEG as taught by Moriyama since Moriyama teach that the PEG-dextran two-phase system may exhibit degradation-controlled protein release and prevent drug diffusion (page 238 first column). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

It has been recently held that "Neither §103's enactment nor *Graham*'s analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art." KSR v. Teleflex, 550 U.S. ___, 82 USPQ2d 1385, 1389 (2007). The KSR court stated that "a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR at 1389.

Furthermore, The KSR court concluded that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in *KSR*

When there is motivation

> "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

In the instant case, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In particular, one would have been motivated to combine the crystallized dextran-insulin composition of Schroder with the PEG component of the composition as taught by Moriyama. Since Moriyama teach that insulin will preferentially partition into the PEG phase (page 238 first full paragraph), the resulting composition meets the limitations of claim 33 of the instant invention. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Further, it is noted that although Moriyama does not expressly teach crystallized dextran, the concentration of 40 wt% of 40000MW dextran used by Moriyama (page 238) could very well result in spontaneous crystallization. For example, Schroder (page 120 last paragraph) and the instant specification (page 5 first paragraph) recognize spontaneous crystallization of dextran. In accord with section 2112.01 I of the MPEP, applicant has the burden of showing why the current product and the prior art product are not the same.

Claims 31,36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schroder (Methods in Enzymology 1985 as cited in IDS) as applied to claims 26-29,32,35,37,41-45 above, and further in view of Ecanow (US 4,963,526 as previously cited).

As discussed above, Schroder teach (page 123) a composition comprising insulin in a crystallized carbohydrate sphere which is made from a solution of dextran T10. Schroder teach that the term crystallization is meant to include hydrogen, and van der Waals interactions, for example (page 119) (compare claim 27 of the instant invention). Using biological assays, Schroder teach that 70% of the radioactivity is entrapped showing that 70% of the insulin is entrapped (page 122 1st full paragraph and page 123). As such, 30% of the insulin is not entrapped. Schroder specifically teach that proteins are not always fully entrapped (page 122 2nd full paragraph). Further, Schroder teach (Figure 2) that all of the insulin is not entrapped as significant portions of the insulin are released over time. Schroder teach aqueous solutions (page 121 last paragraph first sentence) (compare claim 28 of the instant invention). Schroder teach administration via injection (Figure 3 and page 124 last paragraph), so a vessel (such as a syringe) is necessarily required (compare claims 29,35 of the instant invention).

Claim 44 recites a wherein clause (see MPEP 2111.04) that requires the composition to include insulin that is not encapsulated by the microparticles. It is noted that the wherein clause of claim 44 does not specify the degree of encapsulation or how much of the insulin is not encapsulated. Using biological assays, Schroder teach that 70% of the radioactivity is entrapped (in a dextran insulin composition) showing that 70% of the insulin is entrapped (page 122 1st full paragraph and page 123). As such, 30% of the insulin is not entrapped. Schroder specifically

teach that proteins are not always fully entrapped (page 122 2nd full paragraph). Further, Schroder teach (Figure 2) that all of the insulin is not entrapped as significant portions of the insulin are released over time. In summary, Schroder teach the components of claim 44 (crystallized dextran and insulin) as well as meet the limitation of the wherein clause (i.e. at least some of the insulin is not encapsulated).

Claims 41,43, and 45, for example recite properties (porosity and microparticle diameter) that are not reported by Schroder. Please note, since the Office does not have the facilities for examining and comparing Applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. *See In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980), and "as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). In the instant case, the claim product and prior art product are substantially identical in composition (i.e. comprise crystallized dextran and insulin) (see MPEP section 2112.01 I).

Claims 32 and 37 recite compositions comprising shells. Based on the broadest reasonable interpretation of the claim (see MPEP 2111), the insulin entrapped in the crystallized dextran (see page 123) would be a shell meeting the claim limitations.

Claims 42 and 45 recite contacting of insulin with a surface of the dextran. Since the claims are open to any surface of the dextran, Figure 1 of Schroder shows that the protein is in contact with surfaces of the dextran thereby meeting the claim limitations.

Schroder does not expressly teach the composition in the form of tablets.

Ecanow also teach compositions comprising insulin (abstract, claim 1, for example). Ecanow teach that the compositions can be made in the form of tablets (claim 35).

Since Schroder teach the composition for delivery one would be motivated to obtain the composition in various forms for delivery. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

In relation to the recent KSR decision cited above, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In particular, one would have been motivated to combine the form of a tablet as taught by Ecanow with the composition as taught by Schroder thereby meeting the limitations of claims 31 and 36 of the instant invention. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Claims 30,34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schroder (Methods in Enzymology 1985 as cited in IDS) as applied to claims 26-29,32,35,37,41-45 above, and further in view of Clark et al. (US 5,783,556).

As discussed above, Schroder teach (page 123) a composition comprising insulin in a crystallized carbohydrate sphere which is made from a solution of dextran T10. Schroder teach that the term crystallization is meant to include hydrogen, and van der Waals interactions, for example (page 119) (compare claim 27 of the instant invention). Using biological assays, Schroder teach that 70% of the radioactivity is entrapped showing that 70% of the insulin is entrapped (page 122 1st full paragraph and page 123). As such, 30% of the insulin is not entrapped. Schroder specifically teach that proteins are not always fully entrapped (page 122 2nd full paragraph). Further, Schroder teach (Figure 2) that all of the insulin is not entrapped as significant portions of the insulin are released over time. Schroder teach aqueous solutions (page 121 last paragraph first sentence) (compare claim 28 of the instant invention). Schroder teach administration via injection (Figure 3 and page 124 last paragraph), so a vessel (such as a syringe) is necessarily required (compare claims 29,35 of the instant invention).

Claim 44 recites a wherein clause (see MPEP 2111.04) that requires the composition to include insulin that is not encapsulated by the microparticles. It is noted that the wherein clause of claim 44 does not specify the degree of encapsulation or how much of the insulin is not encapsulated. Using biological assays, Schroder teach that 70% of the radioactivity is entrapped (in a dextran insulin composition) showing that 70% of the insulin is entrapped (page 122 1st full paragraph and page 123). As such, 30% of the insulin is not entrapped. Schroder specifically teach that proteins are not always fully entrapped (page 122 2nd full paragraph). Further,

Schroder teach (Figure 2) that all of the insulin is not entrapped as significant portions of the insulin are released over time. In summary, Schroder teach the components of claim 44 (crystallized dextran and insulin) as well as meet the limitation of the wherein clause (i.e. at least some of the insulin is not encapsulated).

Claims 41,43, and 45, for example recite properties (porosity and microparticle diameter) that are not reported by Schroder: Please note, since the Office does not have the facilities for examining and comparing Applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. *See In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980), and "as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). In the instant case, the claim product and prior art product are substantially identical in composition (i.e. comprise crystallized dextran and insulin) (see MPEP section 2112.01 I).

Claims 32 and 37 recite compositions comprising shells. Based on the broadest reasonable interpretation of the claim (see MPEP 2111), the insulin entrapped in the crystallized dextran (see page 123) would be a shell meeting the claim limitations.

Claims 42 and 45 recite contacting of insulin with a surface of the dextran. Since the claims are open to any surface of the dextran, Figure 1 of Schroder shows that the protein is in contact with surfaces of the dextran thereby meeting the claim limitations.

Schroder does not expressly teach the composition with instructions.

Clark teach compositions with insulin (claim 1). Clark further teach kits comprising insulin in which the insulin is in a container (i.e. a vessel) and in which instructions are provided (claim 39) (compare claims 30,34 of the instant invention).

Since Schroder teach the composition for delivery one would be motivated to obtain the composition in various forms for delivery, specifically including instructions for appropriate use and dosage. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Further, it is noted that Section 2112.01 III of the MPEP states that nonfunctional printed matter does not distinguish a claimed product from otherwise identical prior art product.

In relation to the recent KSR decision cited above, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In particular, one would have been motivated to use the kit and instructions as taught by Clark (who also teaches insulin compositions) with the composition as taught by Schroder thereby meeting the limitations of claims 30 and 34 of the instant invention. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ronald T. Niebauer whose telephone number is 571-270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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